Meningococcal B vaccines

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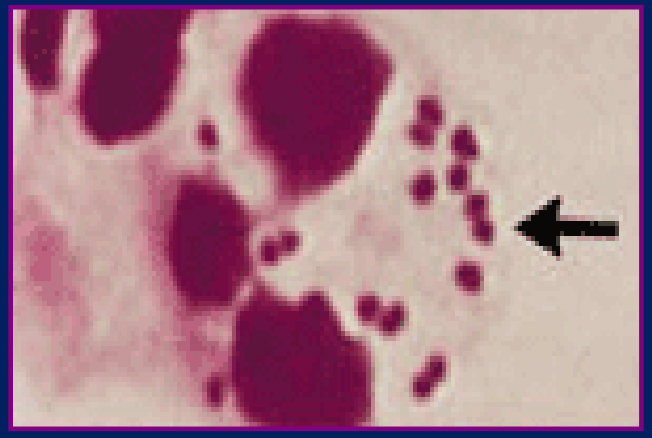
Neisseria meningitidis

- Encapsulated gram-negative diplococcus[1]
- Strictly human pathogen[1]
- Asymptomatic carriage is common
  - Carrier prevalence: 10%–20%[2]
- Transmission[3, 4]
  - Respiratory secretions
  - Direct contact
  - Incubation period: 2–10 days

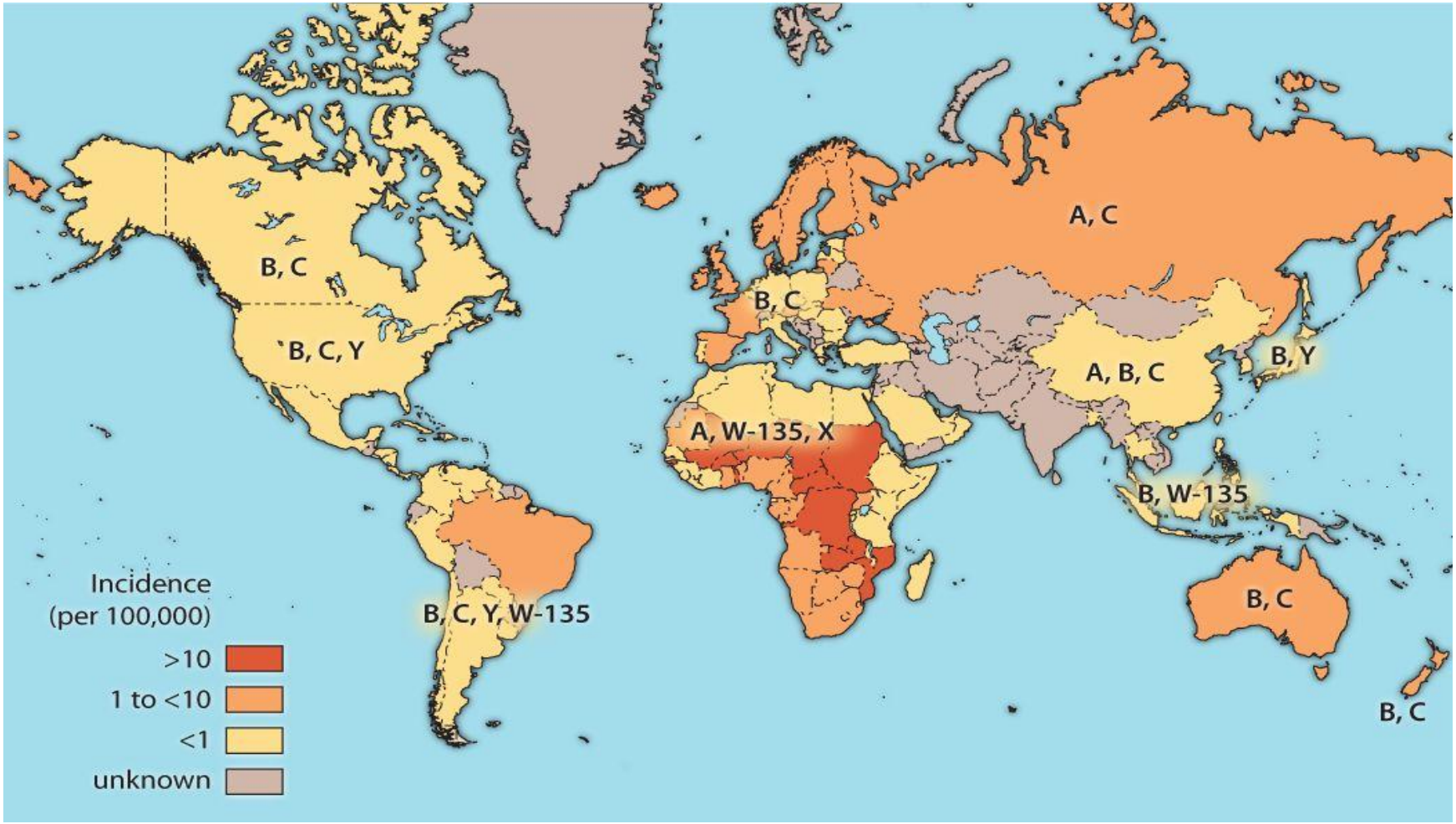


Gram stain of *N. meningitidis* in CSF. Arrow indicates bacterial cells engulfed by neutrophil.[5]

1. van Deuren M, et al. *Clin Microbiol Rev*. 2000;13:144-166; 2. World Health Organization. Meningococcal meningitis factsheet. 2010;
3. Dull PM, et al. *J Infect Dis*. 2005;1919:33-39; 4. WHO. Fact sheet: meningococcal meningitis. 2010;
5. Rosenstein NE, et al. *N Engl J Med.* 2001;344:1378-1388.

Slide courtesy D. McIntosh, Novartis

The scourge of meningococcal disease

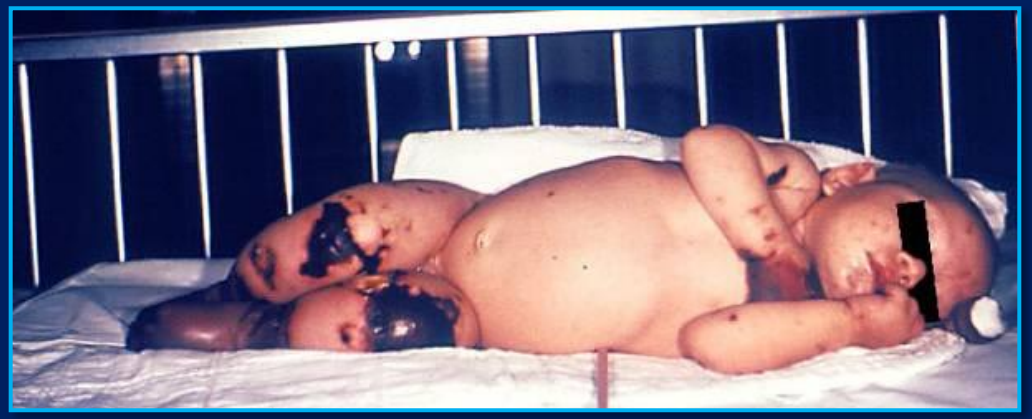


S. Black, M. Pizza, M. Nissum, R. Rappuoli, Toward a meningitis-free world. *Sci. Transl. Med.* **4**, 123ps5 (2012)., slide courtesy R. Rappuoli, Novartis

Invasive Meningococcal Disease

Rapidly progressive, often fatal disease with significant sequelae for many survivors

- Serogroup B meningococcal disease is a feared and often deadly disease, affecting mainly infants
- Is an important cause of invasive bacterial disease globally

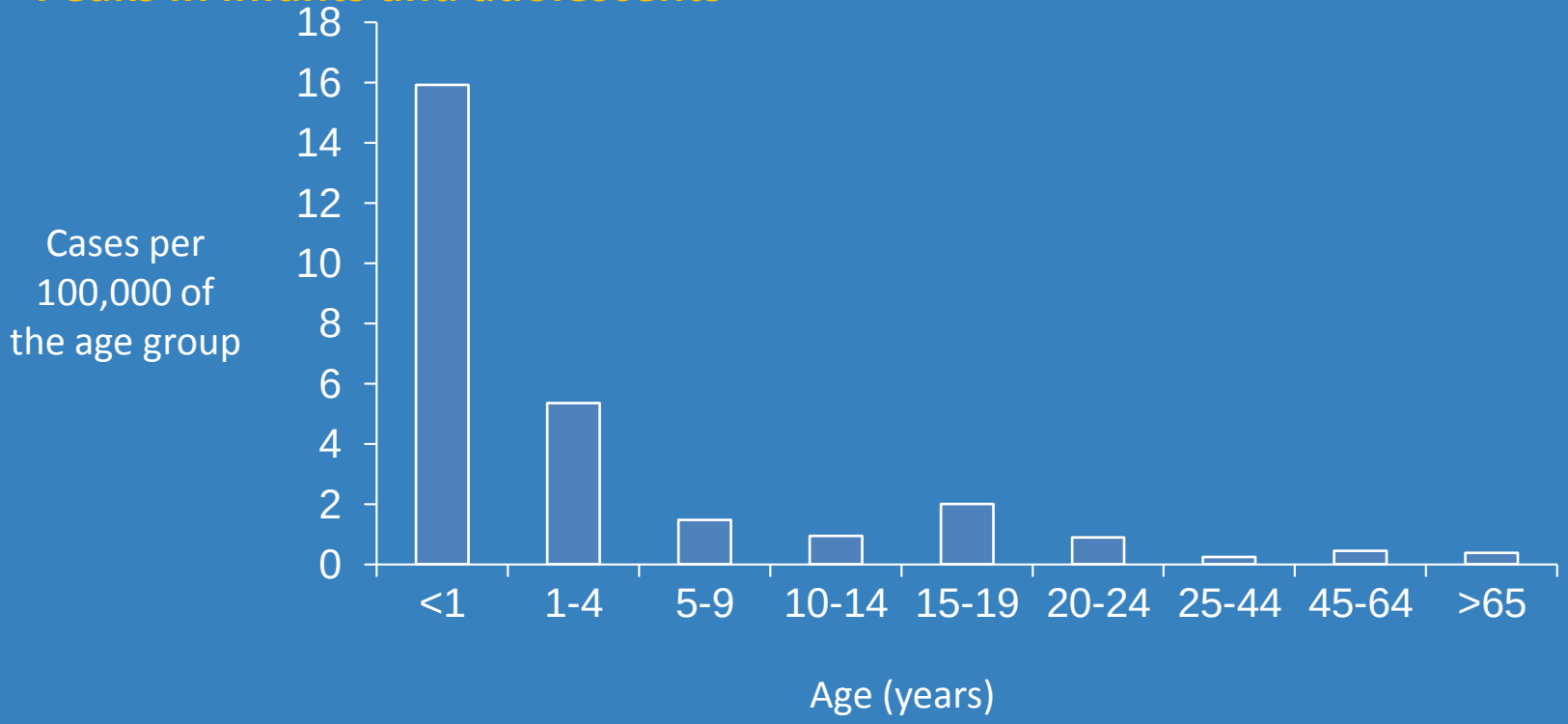


1. Rosenstein NE, et al. *N Engl J Med*. 2001;344:1378-1388; 2. World Health Organization. Meningococcal meningitis factsheet. 2010.
Images in left cluster courtesy of Meningitis Research Foundation UK and are available at www.meningitis.org.
Image of infant on right: Courtesy of Centers for Disease Control and Prevention, available at http://phil.cdc.gov/phil/home.asp.

Slide courtesy D. McIntosh, Novartis

Incidence of Invasive Meningococcal Disease, Europe 2009

- **Peaks in infants and adolescents**



*Countries: Austria, Belgium, Bulgaria, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, Netherlands, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden, United Kingdom, Iceland, and Norway.

European Centre for Disease Prevention and Control. Surveillance of invasive bacterial diseases in Europe 2008/2009. Stockholm: ECDC;2011.

Slide courtesy D. McIntosh, Novartis

Risk Factors

Infants[1-2]

Population with highest incidence

(17.4-fold increase over average in Europe[3])

- Immature immune system
- Reduction of protective maternal antibody levels

Adolescents[4-6]

Population with highest carriage

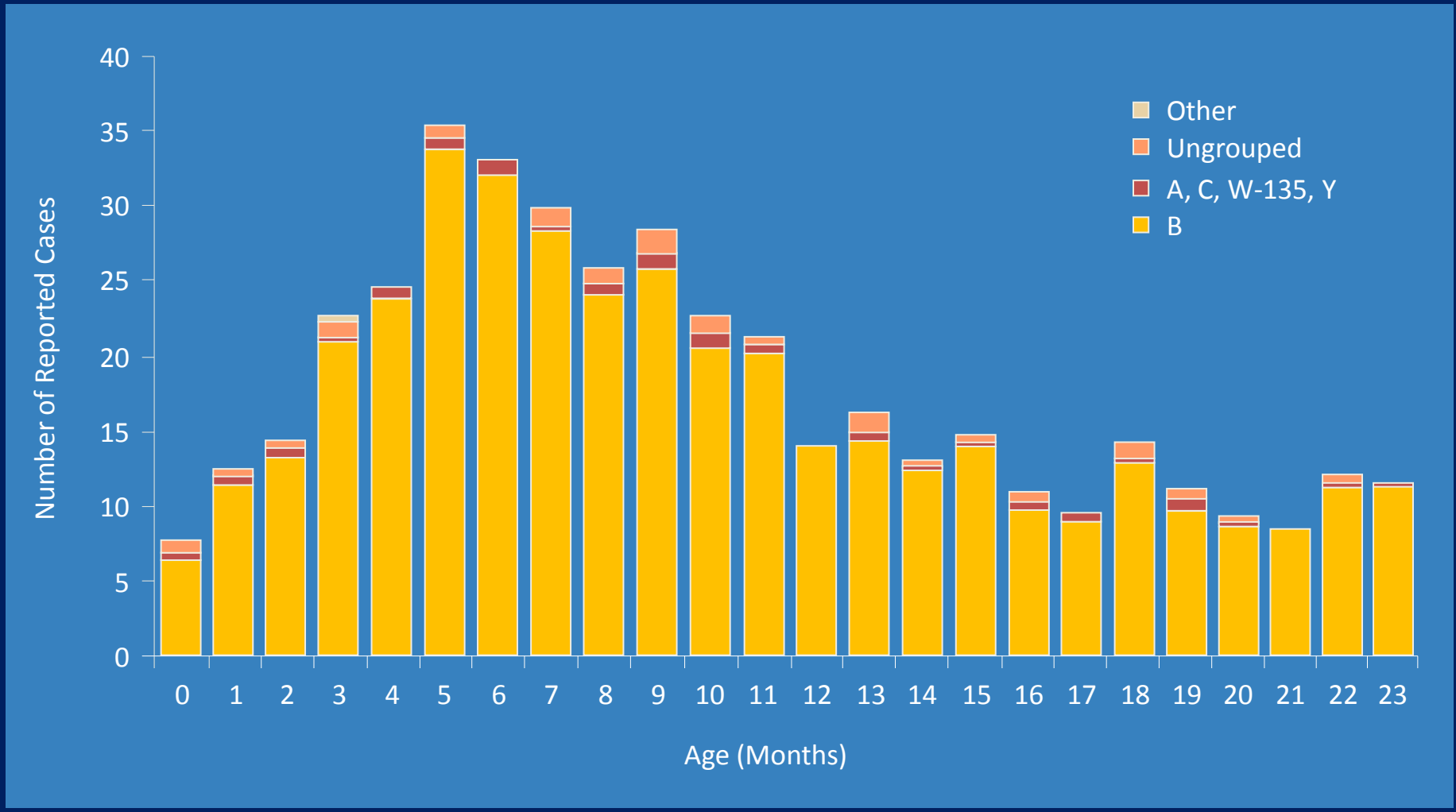
(1.8–5.3-fold increase over other age groups[7])

- Close contact with a case
- Respiratory tract infection
- Smoking
- Crowding
- Dormitory
- Travel
- Concerts

Most cases of meningococcal disease occur in previously healthy persons.

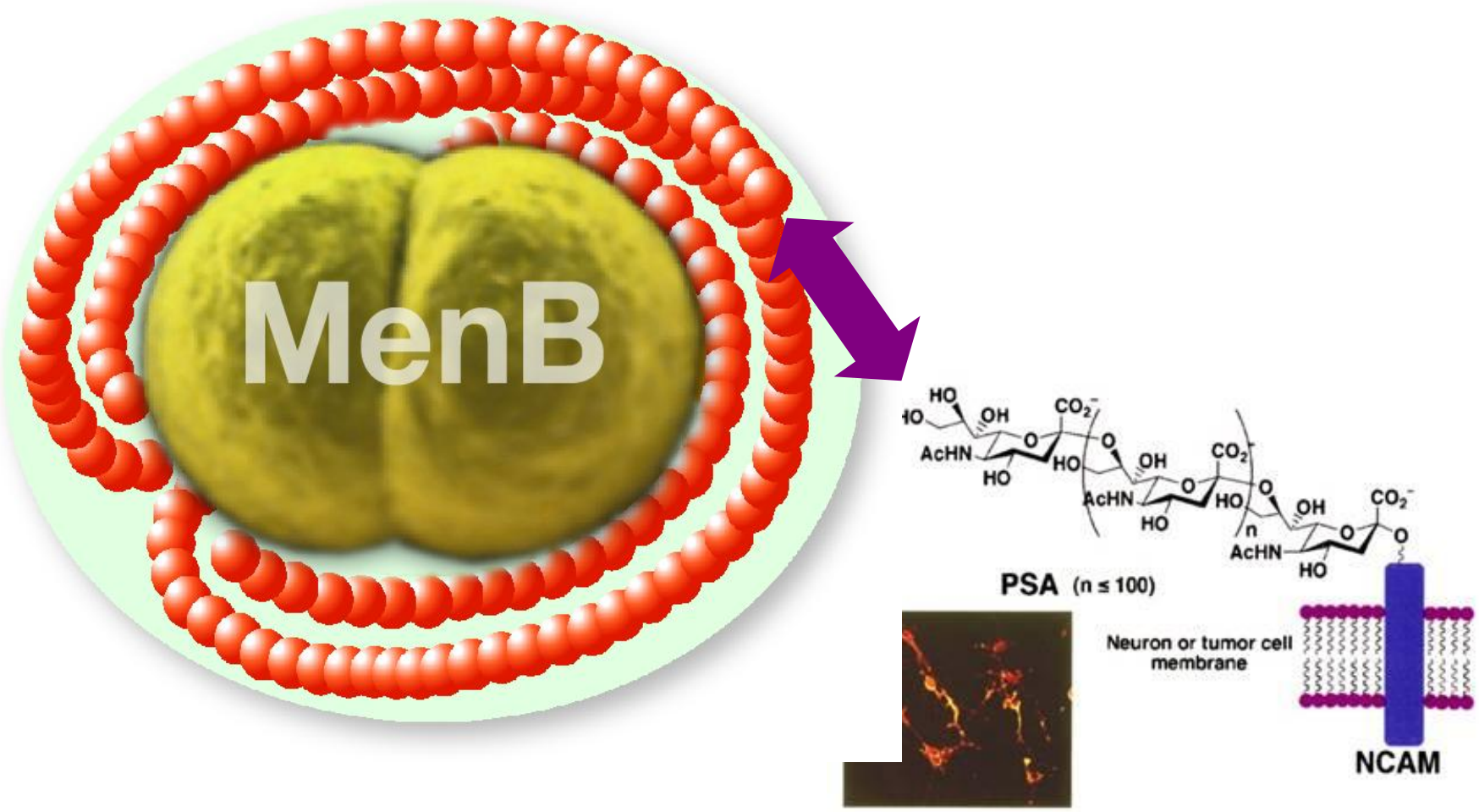
1. Rosenstein NE, et al. *N Eng J Med*. 2001;344:1378-1388; 2. Figueroa JE, et al. *Clin Microbiol Rev.* 1991;4:359-395; 3. European Centre for Disease Prevention and Control. Surveillance of invasive bacterial diseases in Europe 2008/2009. Stockholm: ECDC; 2011; 4. Bilukha OO, et al. *MMWR Recomm Rep.* 2005;54:1-21; 5. Imrey PB, et al. *J Clin Microbiol*. 1995;33:3133-3137; 6. Neal KR, et al. *BMJ.* 2000;320:846-849; 7. Christiansen H, et al. *Lancet Infect Dis*. 2010;10:853–61.

Meningococcal Disease by age and Serogroup, UK 2006-10



Flood J., et al. Presented at 11th European Meningococcal Disease Society meeting, Ljubljana, Slovenia, May 18-20, 2011.

Meningococcus B capsule is a self antigen and cannot be used for vaccination



Slide courtesy R. Rappuoli, Novartis

Approaches to Men B vaccination

- Protein-polysaccharide conjugate
  - Baxter worked on this for years – no human trials
- Outer Membrane Vesicle (OMV)
  - Crude preparation stripped of capsule and cell contents
  - Allowed to form into vesicles in a detergent like reaction
- Also – Transferrin Binding Protein, Por A polyvalent OMV

OMV vaccines

- NIPH Norway
  - Developed in response to men B outbreak in Scandinavia in 1980s
  - Quite reactogenic, two neurological events possibly attributed to the vaccine
  - After a large trial, disease went away
- Finlay Institute, Cuba
  - Similar to NIPH vaccine, perhaps more LPS remaining
  - Based on South American epidemic strain
- Problem is, these vaccines are *strain specific*

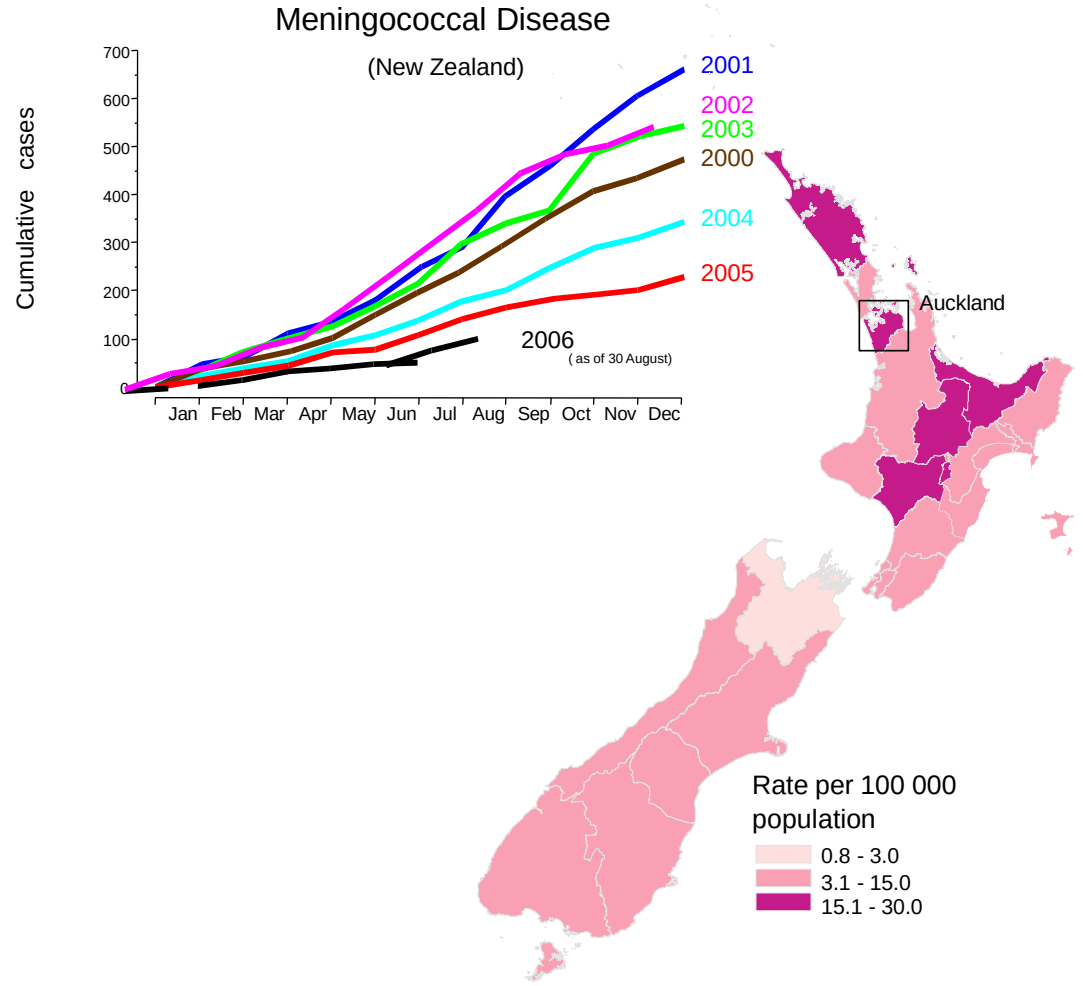
Efficacy of the NIPH OMV Men B vaccine

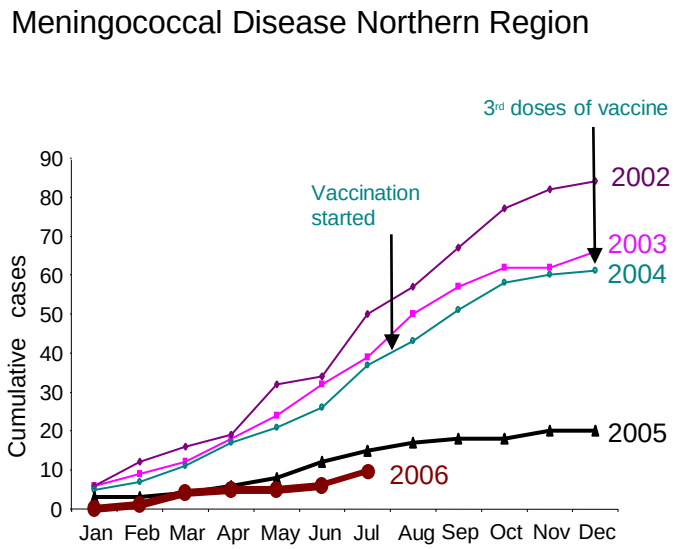
- A placebo controlled, double blind efficacy trial
  - Ra171,800 students volunteered
  - Randomized at school level (1335 secondary schools)
  - Started in October 1988 and the code opened in June 1991
- 36 proven cases of invasive Group B meningococcial disease
  - 12 occurred in eleven schools given vaccine
  - 24 in twenty-four schools given placebo
  - 24 cases were recorded among secondary school students who did not participate
- Vaccine effectiveness was 57% (95% CI 21% to 87%)

Bjune *et al*. Results of an efficacy trial with an outer membrane vesicle vaccine against systemic serogroup B meningococcal disease in Norway. National Institute of Public Health Annals 1991; 14(2): 125-130

Slide courtesy D. McIntosh

New Zealand Meningococcal B epidemic





How was the NZ meningitis epidemic controlled? (1999-2000)

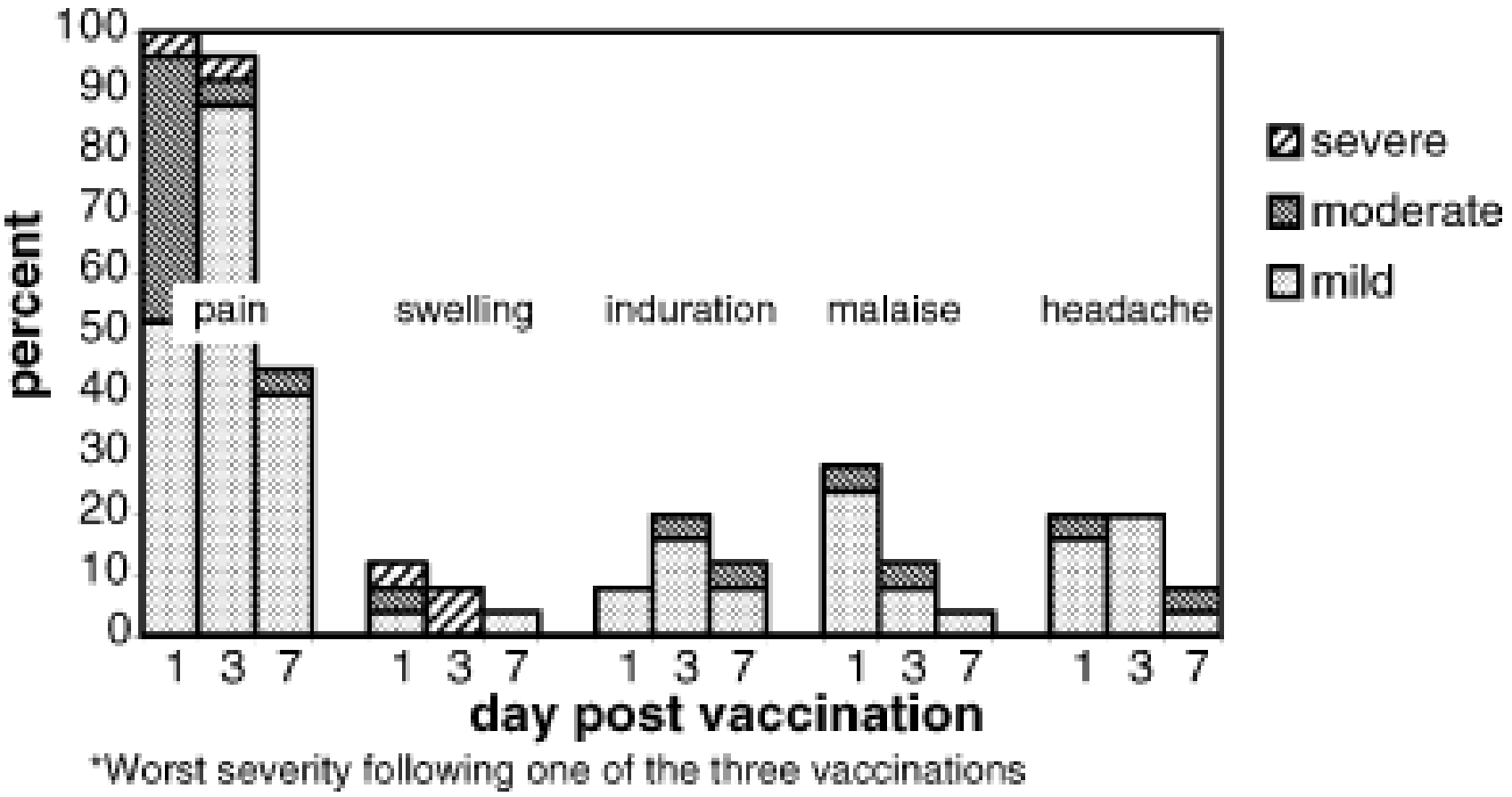
- Choice of vaccine – competitive process
  - Outer membrane vesicle (OMV) vaccine developed by NIPH (Norway) in the 1980s, owned by Chiron
    - Strain specific immunity
  - Needed a vaccine built on B4, P1,4 strain (epidemic strain)
  - Previous NIPH vaccine associated with 2 rare neurological events
  - Technology needed to be moved from Norway to Siena (Italy)
- Is this a new vaccine?

Phase I

- 75 healthy adults in New Zealand (lab workers)
  - 25 received MeNZB 50 µg/ml
  - 24 received MeNZB 25 µg/ml
  - 26 received MenBvac 25 µg/ml (“parent vaccine”)
- Reactogenicity and adverse events monitored
- Complex analysis of antibody responses
  - SBAs using various targets and methods
  - ELISA assays with various targets

Clinical and Vaccine Immunology 2007;14:830-8.

Phase 1 – results - reactogenicity



Vaccine 2006;24:1395-1400.

Phase 1 – results - immunogenicity

Serum bactericidal antibody seroresponders to selected meningococcal group B strains in healthy adults by strain and vaccine[a]

Vaccine	Post dose	Number	Strain			
			NZ98/254 (%)	NZ02/09 (%)	NZ94/167 (%)	H44/76 (%)
NZ candidate vaccine 25 μg	1	24	63[b]	46	38	29
	2	23	87[b]	78	70	43
	3	23	100[b]	87	83	48
NZ candidate vaccine 50 μg	1	23	65	48	57	30
	2	23	78	70	78	35
	3	23	87	83	78	43
MenB vac™ 25 μg	1	24	33	21	42	54[b]
	2	25	44	28	52	52[b]
	3	26	42	35	54	65[b]

[a] A seroresponder is defined as a participant who shows at least a four-fold increase in serum bactericidal antibody compared to their baseline (pre-vaccination) measure, with a titre <2, i.e. below the detection limit, assigned a value of one and using a continuous scale of titre values.(interpolated titres).

[b] The response measured to the strain from which the vaccine was derived.

Vaccine 2006;24:1395-1400.

Phase 1 – conclusions for MeNZB

- Safe and immunogenic
- Similar reactogenicity profile to parent vaccine
- SBA using epidemic strain most appropriate test of immunogenicity
- Dose of 25 µg/ml appropriate

Phase 2 sequence planned

- Schoolchildren 8-12 years of age
- Toddlers 16-24 months of age
- Infants 6-8 months of age
- Infants 6 weeks of age

Immunogenicity by age group

Percentage of seroresponders to MeNZB ™ in each age-group study as measured by SBA using NZ98/254 as target strain

Age group	Variable	MeNZB ™	Control
Adults	N	24	26
	% responders[a]	96	42
	95% CI	79–100	23–63
8–12 years old	*N*	485	56
	% responders[a]	76	32
	95% CI	72–80	20–46
16–24 months old	*N*	231	55
	% responders[a]	75	4
	95% CI	69–80	0–13
6–8 months old	*N*	201	52
	% responders[a]	74	0
	95% CI	67–80	0–7

[a] Seroresponders are defined as subjects showing at least a four-fold increase in SBA antibody titres from day 1. If titre is <4 on day 1, one needs a titre of 8 to be considered a responder.

Vaccine 2005;23:2191-6

Immunogenicity in young infants

TABLE 2. Immune Response Against NZ98/254 in Healthy Infants Aged 6 to 10 Weeks Vaccinated With 3 and 4 Doses of MeNZB

	MeNZB + Routine % (95% CI) n	Routine % (95% CI) n	4 Doses MeNZB % (95% CI) n
Seroresponders*			
Post dose 3 (day 161)	83 (46–89) 239†	0 (0–4) 120‡	46 (33–58) 80§
Pre dose 4 (day 266)			14 (7–26) 51
Post dose 4 (day 298)			69 (54–80) 48
Serum bactericidal titers ≥1:4			
Preimmunization (day 1)	8 (5–12) 250	9 (5–15) 126	7 (2–17) 51
Post dose 3 (day 161)	76 (70–81) 239†	0 (0–4) 120‡	74 (61–84) 80§
Pre dose 4 (day 266)			27 (17–41) 51
Post dose 4 (day 298)			82 (68–91) 48¶

Pediatr Infect Dis J 2009;28:385-90.

Immunogenicity conclusions

- 3 doses of 25 µg/ml appropriate for all but young infants
- Young infants required a 4th dose to achieve acceptable immunogenicity
- Immunogenicity of routine vaccines was unaffected by co-administration of MeNZB

Reactogenicity in young infants

TABLE 5. Percentage of Local and Systemic Reactions After Immunization of Healthy Infants Aged 6 to 10 Weeks With 4 Doses of MeNZB

Reaction	Dose 1 n = 51 % (95% CI)	Dose 2 n = 51 % (95% CI)	Dose 3 n = 51 % (95% CI)	Dose 4 n = 50* % (95% CI)
Local reactions				
Erythema ≥10 mm	16 (8–28)	8 (3–19)	8 (3–19)	52 (39–65)
Induration ≥10 mm	20 (11–33)	6 (1–17)	4 (0–14)	58 (44–71)
Swelling ≥10 mm	8 (3–19)	4 (0–14)	2 (0–11)	24 (14–38)
Tenderness	59 (45–71)	49 (36–62)	39 (27–53)	48 (35–61)
Systemic reactions				
Irritability	90 (78–96)	88 (76–95)	65 (51–76)	60 (46–72)
Sleepiness	67 (53–78)	59 (45–71)	39 (27–53)	32 (21–46)
Change in eating habits	41 (29–55)	29 (19–43)	24 (14–37)	16 (8–29)
Vomiting	24 (14–37)	18 (9–31)	10 (4–22)	8 (3–19)
Diarrhoea	16 (8–28)	18 (9–31)	10 (4–22)	10 (4–22)
Unusual crying	61 (47–73)	53 (40–66)	20 (11–33)	20 (11–33)
Rash	10 (4–22)	14 (7–26)	14 (7–26)	14 (7–27)
Fever ≥38°C	24 (14–37)	37 (25–51)	16 (8–28)	26 (16–40)
Fever ≥39°C	0 (0–9)	8 (3–19)	2 (0–11)	4 (0–14)
Analgesic use	61 (47–73)	67 (53–78)	55 (41–68)	48 (35–61)

Pediatr Infect Dis J 2009;28:385-90.

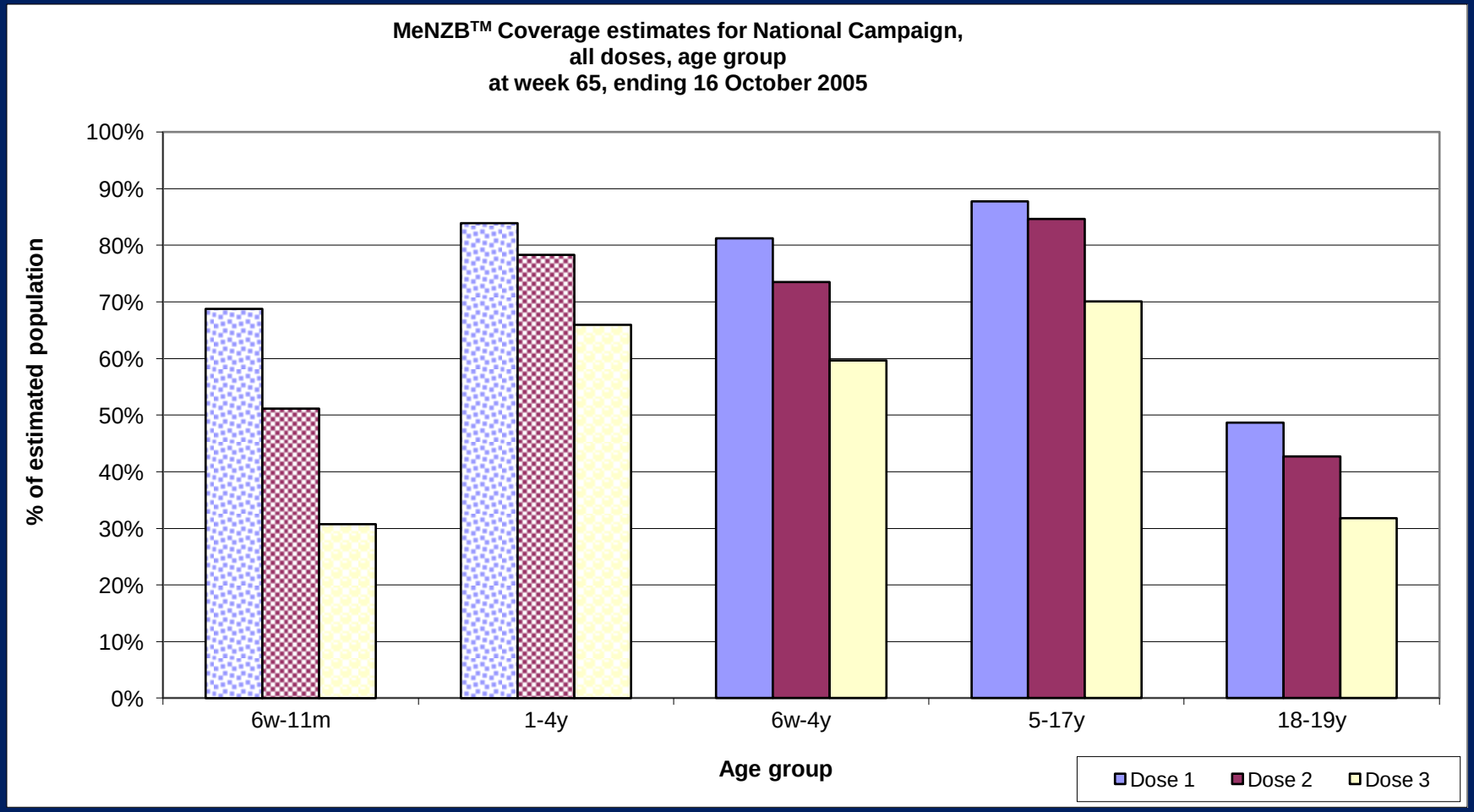
Reactogenicity conclusions

- High frequency of local and systemic reactions in all age groups
  - Most mild or moderate
  - Local pain most common problem
  - Better tolerated in young infants than other age groups

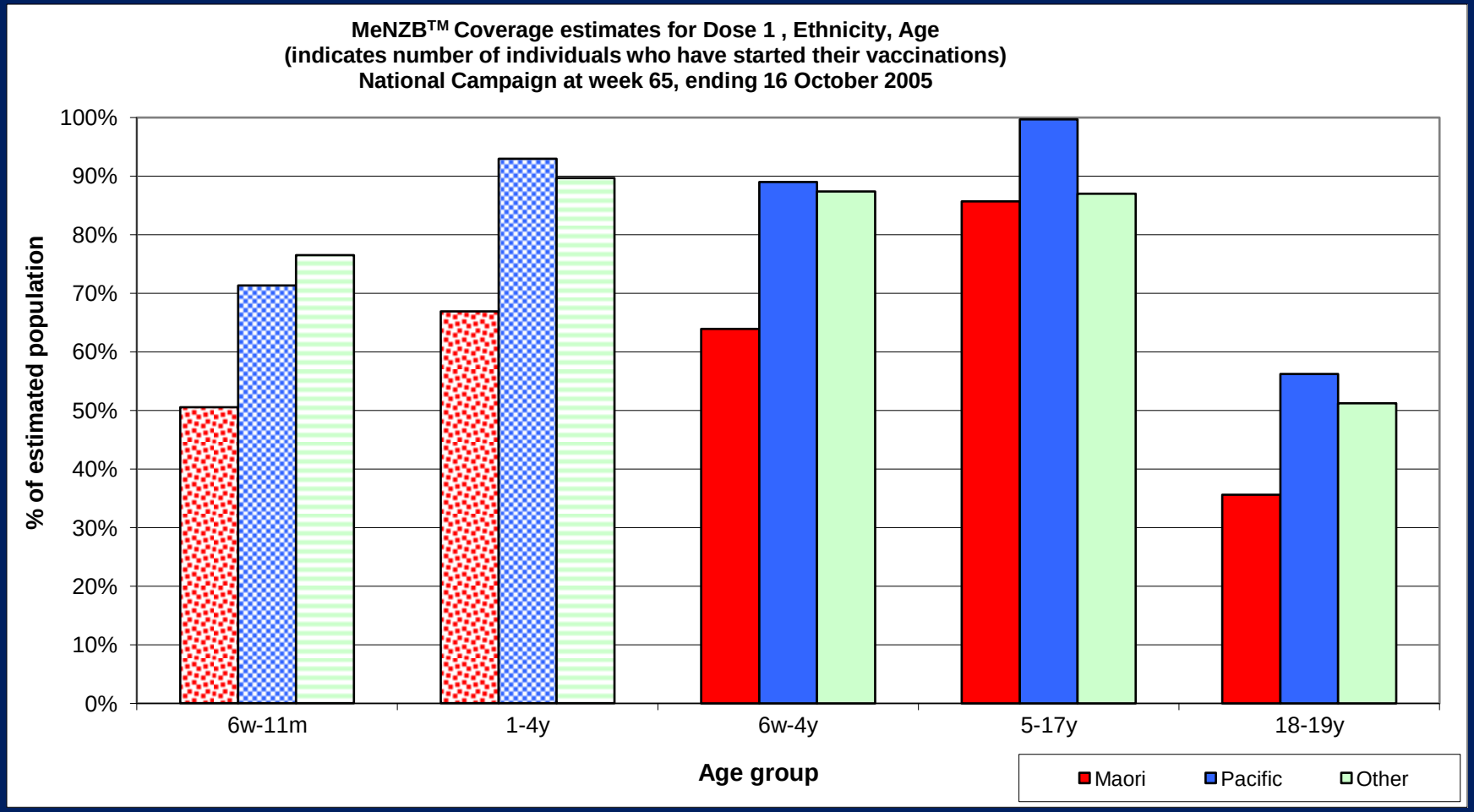
MeNZB post-script

- The vaccine was rolled out for all under 20 years of age in New Zealand
- Most affected areas covered first
- High coverage rates in Maori and Pacific Islander communities
- Disease rapidly disappeared
- Vaccine effectiveness estimated to be 83%
- Vaccination ceased in 2006

MeNZ-B coverage by age and dose



MeNZ-B coverage by ethnicity and age



MeNZB post-script - safety

Table 1 **Event terms most frequently reported to CARM following meningococcal B vaccination, aged <20 years, July 19, 2004 to June 30, 2006, New Zealand**

Event	Number of Reports* Received to June 30, 2006	Proportion of Total Reports* (n = 2212) to June 30, 2006 (%)
Local injection site events	925	41.8
Skin-related events	804	36.3
Fever	705	31.9
Gastrointestinal symptoms	577	26.1
Headache	250	11.3
Musculoskeletal	165	7.5
Irritability	122	5.5
Syncope/fainting	88	4.0
Sleepiness/somnolence	81	3.7
Seizure (non-febrile)	33	1.5
Febrile seizure	27	1.2

*Each report may include more than one event, therefore the proportion of all reports will total to >100%.

Vaccines, 2007;3:196-204

MeNZB post-script - safety

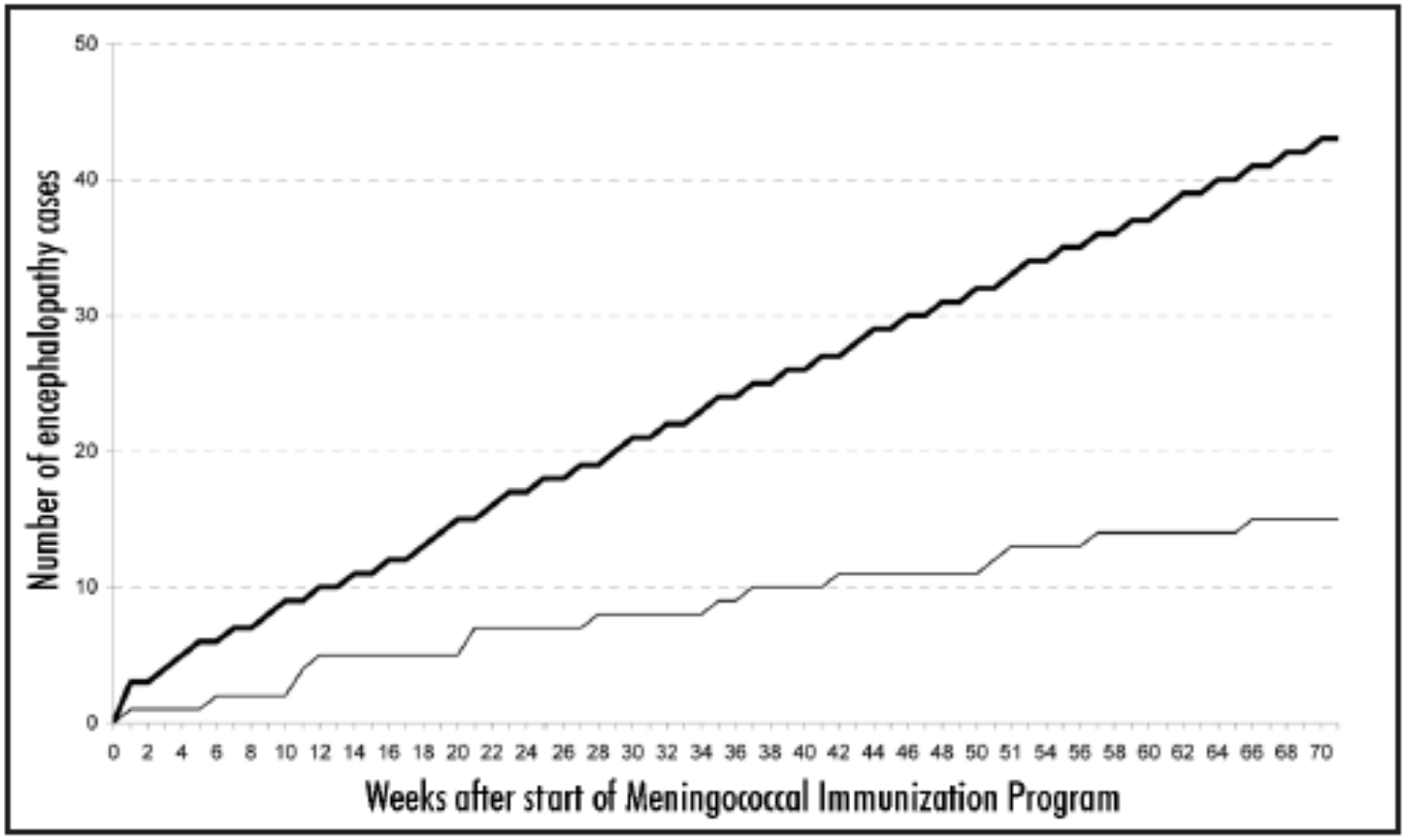


Figure 2. Number of observed and expected encephalopathy cases in the hospital surveillance area, aged <5 years, July 19, 2004 to November 27, 2005, New Zealand. 1st line, threshold*; 2nd line, number of observed encephalopathy case. *Upper bound of the expected number of cases, based on the cumulative 95% binomial distribution.

Human Vaccines, 2007;3:196-204

MeNZB post-script - safety

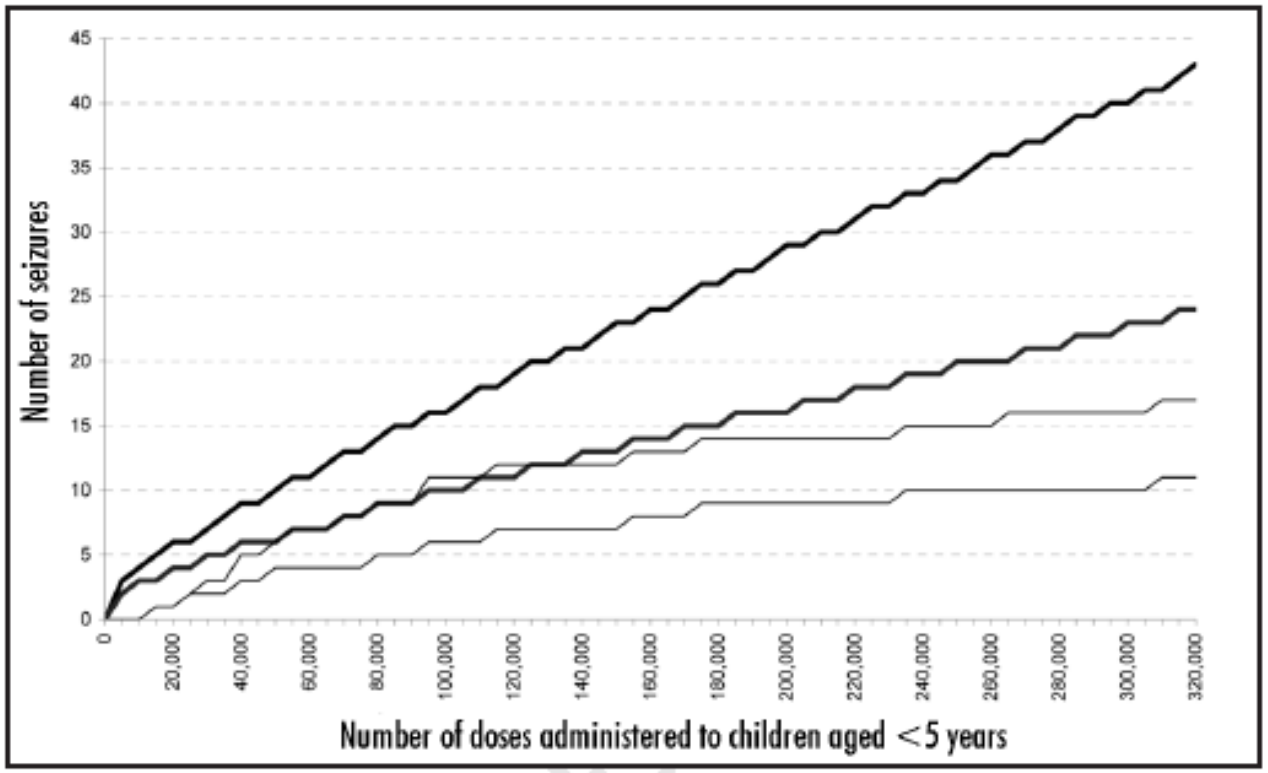
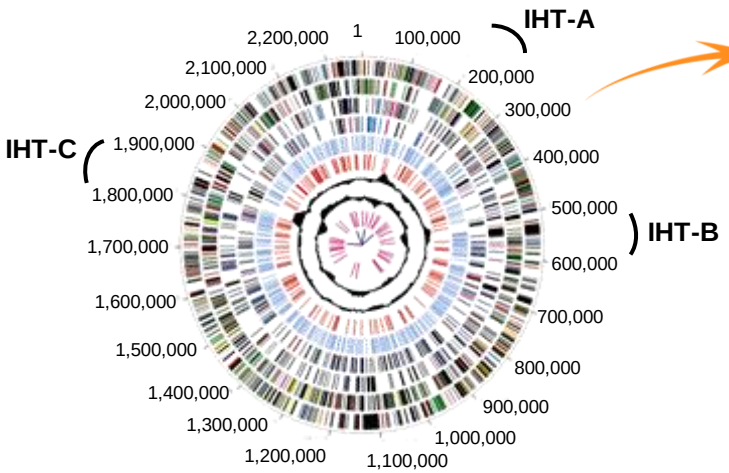


Figure 3. Number of observed and expected seizures occurring within four days after meningococcal B vaccination in the hospital surveillance area, aged <5 years, July 19, 2004 to November 27, 2005, New Zealand. 1st line, 1 per 10,000 doses threshold*; 2nd line; 1 per 20,000 doses threshold*; 3rd line, total number of observed seizures; 4th line, number of observed simple febrile seizures. *Upper bound of the expected number of cases, based on the cumulative 95% binomial distribution.

Human Vaccines, 2007;3:196-204

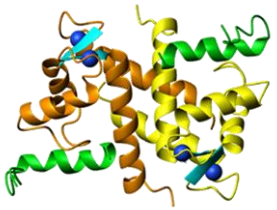
Novartis approach - Reverse Vaccinology for the Identification of Immunogenic MenB Antigens

Based on the genome sequence of MC58, 600 ORFs that potentially encoded novel surface exposed or exported proteins were identified



expression and purification

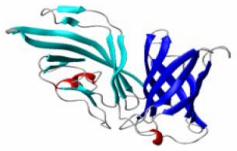
~350 proteins successfully expressed in *E.coli*, purified, and used to immunize mice



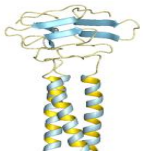
purified proteins

immunizations

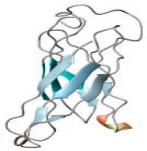
Testing for bactericidal activity



fHbp variant 1



NadA

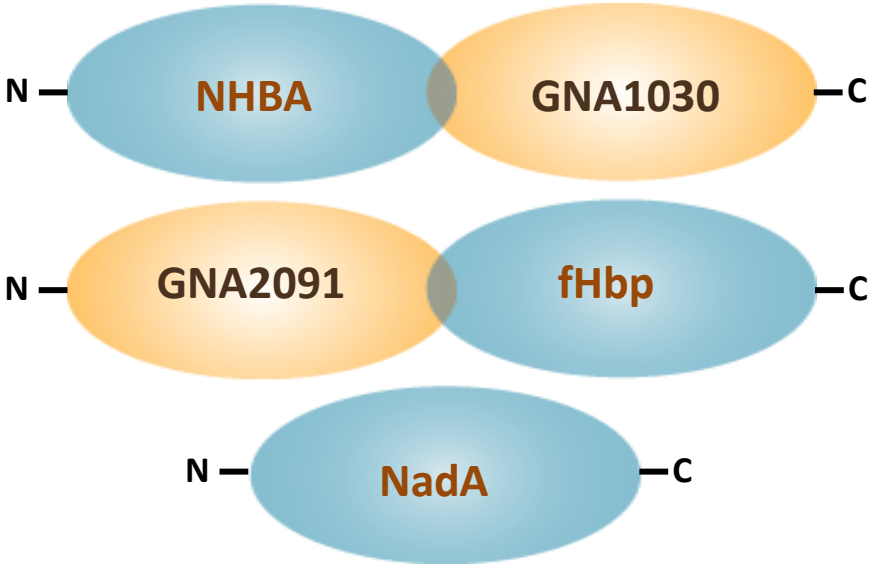


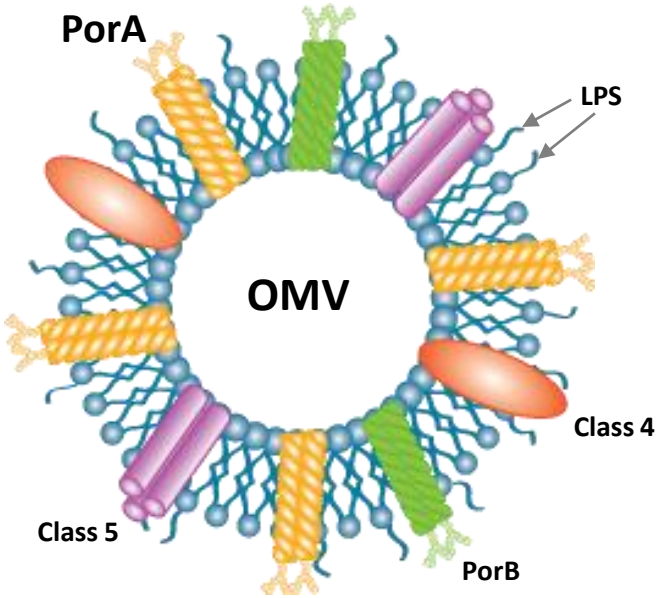
NHBA

Pizza M. et al. Science 2000

4CMenB Vaccine Composition

- Three protein antigens (two fusion proteins and one single polypeptide)
- Outer Membrane Vesicle (OMV) component (NZ PorA is P1.4)





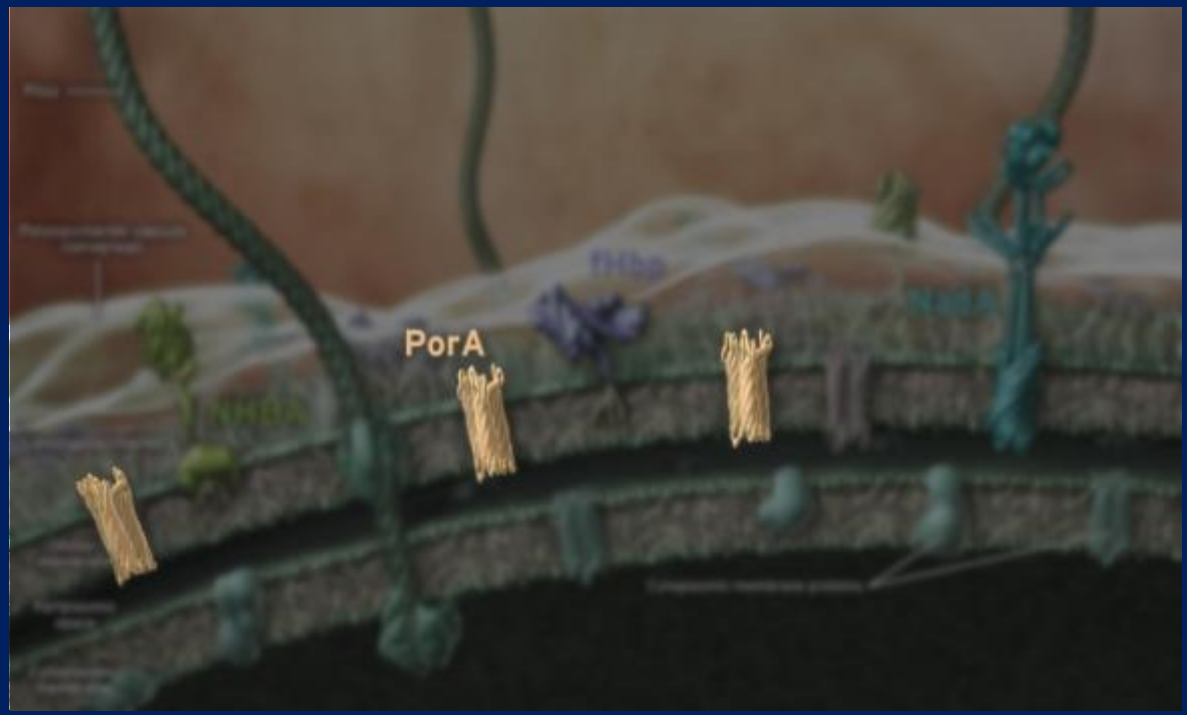
- 4CMenB is a suspension for injection

Dose	NHBA-GNA1030	fHbp-GNA2091	NadA	OMV	Al^{3+}
0.5ml	50 µg	50 µg	50 µg	25 µg	0.5 mg

Components of the 4CMenB

(from D. McIntosh, Novartis)

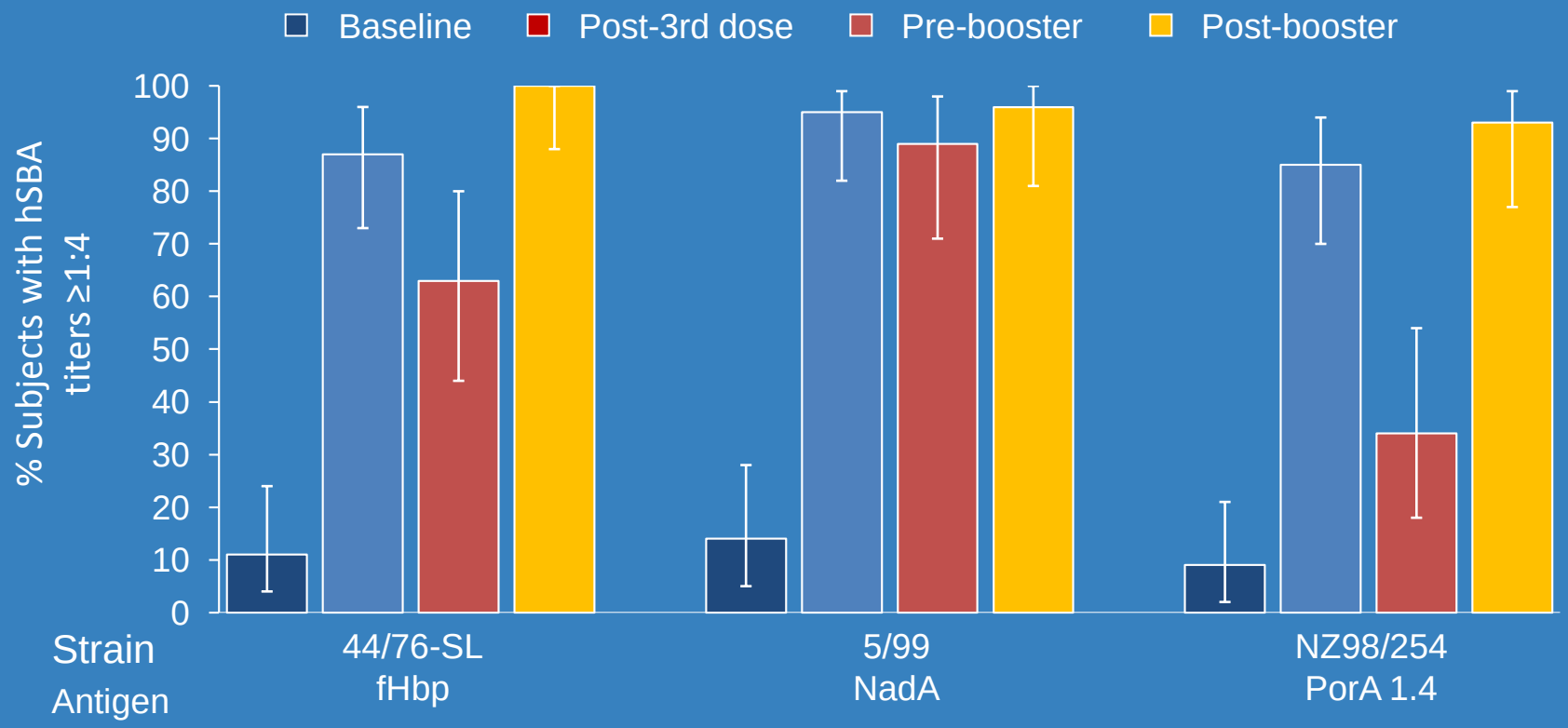
- **NadA: neisserial adhesin A**
  - Promotes adherence to and invasion of human epithelial cells[1-3]
  - Possible importance in carriage
- **fHbp: factor H binding protein**
  - Binds the bacterial siderophore enterobactin *(in vitro)*[4]
  - also binds factor H, which enables bacterial survival[5,6]
- **NHBA: Neisseria heparin-binding antigen**
  - Present in virtually all strains
  - Binds heparin, which may increase the serum resistance of bacteria[7-9]
- **NZ PorA 1.4: porin A**
  - Major outer membrane vesicles protein
    - produces robust antibody response



1. Comanducci M, et al. *J Exp Med*. 2002;195:1445-1454; 2. Capecchi B, et al. *Mol Microbiol*. 2005;55:687-698; 3. Mazzon C, et al. *J Immunol*. 2007;179:3904-3916; 4. Veggi D, et al. Presented at IPNC. Banff, Canada. September 11-16, 2010; 5. Madico G, et al. *J Immunol.* 2006;177:501-510; 6. Schneider MC, et al. *J Immunol*. 2006;176:7566-7575; 7. Serruto D, et al. *Proc Natl Acad Sci U S A*. 2010;107:3770-3775; 8. Welsch JA, et al. *J Infect Dis*. 2003;188:1730-1740; 9. Plested, et al. *Clin Vaccine Immunol*. 2008;15:799-804.

4CMenB Immunogenicity in Infants

- **4CMenB was immunogenic in infants when given in a 3-dose primary series at 2-4-6 plus a booster at 12 months of age**



Phase II in Infants
Study V72P6 in the UK

hSBA = serum bactericidal assay using human complement 1 month postvaccination; n=46.

Findlow J, et al. *CID.* 2010;51:1127-1137.

The Meningococcal Antigen Typing System (MATS)

- MATS is a system of analysis to determine, for a country or region, what proportion of strains are covered by the vaccine
- MATS examines the 3 antigen components of 4CMenB (fHbp, NadA, and NHBA) against 2 criteria:
  1. Antigen quantity
  2. Similarity of strain antigens to vaccine antigens
- Positive Bactericidal Threshold (PBT) is established for each protein antigen

  = the minimum amount of susceptible antigen needed to result in killing in the Serum Bacteriocidal Assay
- For PorA, PCR is used to determine the similarity of the PorA in the test strains to that in the vaccine

MATS: A Simple Calculation Assesses Strain Coverage per Region

- Strains are estimated to be covered if either one of two criteria are met:
  - Any protein antigen is expressed above the PBT
  - The PorA gene is matched to that which is in 4CMenB

EXAMPLE:

	Bacterial strain #									
	1	2	3	4	5	6	7	8	9	10
fHbp >PBT	✓	✓		✓			✓		✓	✓
NHBA >PBT		✓	✓		✓		✓		✓	✓
NadA >PBT										✓
PorA 1.4 matched		✓								✓

$\frac{8}{10}$ = 80% strain coverage

MATS results for Europe

- Based on > 1,000 MenB strains


Norway: 85% [95% CI: 83%, 100%]


England & Wales: 73% [60%, 90%]


Germany: 81% [71%, 93%]


France: 83% [73%, 95%]


Italy: 87% [75%, 94%]

*Norway: n=41; France: n=200; Germany: n=222; Italy: n=54; England and Wales: n=535.
†Coverage based on MATS from pooled sera from 13-mo-old infants vaccinated at 2,4, 6, and 12 mo of age tested on 1,011 strains isolated during the 2007-2008 epidemiological year.

Donnelly J. Presented at: 11th meeting of The European Meningococcal Disease Society (EMGM); 18-20 May 2011; Ljubljana, Slovenia.

Bivalent rLP2086 vaccine (Pfizer)

- LP2086 - Factor H-binding protein
  - a lipoprotein expressed on the surface of all meningococcal serogroups
  - 2 serologically distinct subfamilies (A and B)

Bivalent rLP2086 vaccine

- Clinical trials of 11-40 year olds in Spain, Australia, Poland
  - High hSBA responses were observed regardless of LP2086 subfamily, subgroup, variant, or other epidemiologic markers
  - Robust bactericidal activity was demonstrated against diverse MnB hSBA test strains
    - » These represent around 90% of LP2086 variants responsible for invasive MnB and >75% of LP2086 variants from carriage isolates
- Phase 1 trial of rLP2086 completed in Australian toddlers

Where to now with Men B vaccination?

- Major remaining meningitis vaccine target
- One or both vaccines may be ready for licensure soon (within 12 mths)
- Phase 3 (efficacy) trial considered non-feasible
- Licensure will be based on SBA data (immunogenicity)